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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/790,768	03/03/2004	Michael Karas	002877.00028	3188

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EXAMINER	
DESAI, ANAND U	
ART UNIT	**PAPER NUMBER**
1653	

DATE MAILED: 02/24/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/790,768	KARAS, MICHAEL	
	Examiner	Art Unit	
	Anand U. Desai, Ph.D.	1653	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *21 November 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-30* is/are pending in the application.

4a) Of the above claim(s) *4-6,10-12 and 14-28* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3,7-9,13,29 and 30* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *20040603, 20040813*, 20050304.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

1. Applicant's election without traverse of Group V, claims 29, and 30, drawn to a polypeptide comprising a chemical cross-linker in the reply filed on November 21, 2005 is acknowledged. Applicant's species election of a small molecule as a cargo moiety is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

2. The requirement is still deemed proper and is therefore made FINAL.

3. Claims 4-6, 10-12, and 14-28 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected inventions, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on November 21, 2005.

4. Claims 1-3, 7, 8, 9, 13, 29, and 30, which are drawn to the elected invention, are currently pending and are under examination.

Priority

5. Acknowledgment is made of applicant's claim for priority under 35 U.S.C. 119(e). The priority date is March 4, 2003.

Information Disclosure Statement

6. The information disclosure statements (IDSs) submitted on August 13, 2004, June 3, 2004, and March 4, 2005 are being considered by the examiner.

Claim Rejections - 35 USC § 112

7. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

8. Claims 7-9, and 13 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

9. In claim 7, how is the protein transduction domain "linked" to a cargo moiety?

10. In claim 9, how is an atom, "radionuclide", also a small molecule?

11. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

12. Claims 1-3, 7-9, 13, 29, and 30 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a complex comprising a polypeptide consisting of SEQ ID NO: 2 (SEQ ID NO: 1 with amino acid linker, including a lysine reactive side chain moiety) covalently linked with a biotin, and either an avidin conjugated β-galactosidase or avidin conjugated alkaline phosphatase that can transduce HEK 293 (human embryonic kidney), human umbilical vein endothelial, and NIH 3T3 fibroblast cells, does not reasonably provide enablement for any complex comprising a polypeptide consisting of SEQ ID NO: 1 or SEQ ID NO: 2, and any cargo moiety that can transduce any cell. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

In *In re Wands*, 8 USPQ2d 1400 (Fed. Cir., 1988) eight factors should be addressed in determining enablement.

1.) The nature of the invention: the invention is drawn to an isolated and purified polypeptide with a protein transduction domain which comprises SEQ ID NO: 1. The transduction domain is implied to have the utility of transporting the cargo moiety. The invention is also drawn to a complex comprising a polypeptide with a protein transduction domain linked to a cargo moiety, wherein the protein transduction domain comprises SEQ ID NO: 1, and the cargo moiety is selected from a group consisting of a small molecule, a nucleic acid, and a polypeptide.

2.) The breadth of the claims: the claims are extremely broad for the isolated and purified polypeptide with a protein transduction domain, because it can be reasonably interpreted to encompass peptides located on the amino or carboxy terminus of the protein transduction domain. The claims are extremely broad in that a very large number of constituents could be encompassed by the cargo moiety. Furthermore, no limitation is placed on the utility of the complex in terms of the cell that can be transduced by the protein transduction domain.

3.) The predictability or unpredictability of the art: / 7.) The state of the prior art: there is unpredictability in the art with regard to the transduction of cells using protein transduction domains. Applicants specification describes the alteration in transduction efficiency of a β-galactosidase when the protein transduction domain is located on the amino- or carboxy-terminus relative to the reporter polypeptide (see page 19, paragraph [74]), and the difference in translocation efficiency when a nuclear localization is attached to either the amino- or carboxy-terminus of the protein transduction domain (see page 24, paragraph [91]). Falnes et al. has

described experiments with fusion proteins of protein transduction domain molecules, e.g. VP22, conjugated with diphtheria toxin A-fragment, which are not translocated into Vero cells (see Falnes et al., particularly page 4354, Results, Characterization of a Fusion Protein between VP22 and dtA section, and page 4356, Figure 7B). Violini et al. describe the complete lack of intracellular accumulation of fluorescein conjugated TAT-peptides in MDCK and CaCo-2 cells (see Violini et al. Biochemistry 41: 12652-12661, see Abstract and 2nd paragraph of Discussion). Thus, there is no way to predict whether protein transduction domain molecules will mediate the translocation of any cargo moiety into any cell.

4.) & 5.) The amount of direction or guidance presented:/The presence or absence of working examples: the examples of complexes comprising the protein transduction domains identified by SEQ ID NOs do not in any way suggest that all cargo moieties can be translocated across biological membranes. The specification provides guidance with respect to specific protein transduction domains (identified by SEQ ID NOs: 14 and 16 that comprise SEQ ID NO: 1) with cargo moieties consisting of either β-galactosidase or alkaline phosphatase to transfect HEK 293, HUVEC, and NIH 3T3 cells. The working examples provide no guidance whatsoever in selecting other cargo moieties, which might have the needed structure for translocation across the breadth of cells encompassed by the currently claimed invention.

6.) The quantity of experimentation necessary: there is a large quantity of experimentation necessary to determine which cargo moieties can be translocated in which cells.

8.) Level of skill in the art: the level of skill in this art is high, at least that of a doctoral scientist with several years of experience in the art.

In consideration of each of factors 1-8, it is apparent that there is undue experimentation because of variability in prediction of outcome that is not addressed by the present application disclosure, examples, teaching, and guidance presented. Absent factual data to the contrary, the amount and level of experimentation needed is undue.

13. Claims 1-3, 7-9, 13, 29, and 30 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The MPEP states that the purpose of the written description requirement is to ensure that the inventor had possession, at the time the invention was made, of the specific subject matter claimed. The courts have stated:

> "To fulfill the written description requirement, a patent specification must describe an invention and do so in sufficient detail that one skilled in the art can clearly conclude that "the inventor invented the claimed invention." *Lockwood v. American Airlines, Inc.*, 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (Fed. Cir. 1997); *In re Gostelli*, 872 F.2d 1008, 1012, 10 USPQ2d 1614, 1618 (Fed. Cir. 1989) ("[T]he description must clearly allow persons of ordinary skill in the art to recognize that [the inventor] invented what is claimed."). Thus, an applicant complies with the written description requirement "by describing the invention, with all its claimed limitations, not that which makes it obvious," and by using "such descriptive means as words, structures, figures, diagrams, formulas, etc., that set forth the claimed invention." *Lockwood*, 107 F.3d at 1572, 41 USPQ2d at 1966." *Regents of the University of California v. Eli Lilly & Co.*, 43 USPQ2d 1398.

Further, for a broad generic claim, the specification must provide adequate written description to identify the genus of the claim. In *Regents of the University of California v. Eli Lilly & Co.* the court stated:

> "A written description of an invention involving a chemical genus, like a description of a chemical species, 'requires a precise definition, such as by structure, formula, [or] chemical name,' of the claimed subject matter sufficient to distinguish it from other materials." *Fiers*, 984 F.2d at 1171, 25 USPQ2d 1601; *In re Smythe*, 480 F.2d 1376, 1383, 178 USPQ 279, 284985 (CCPA 1973) ("In other cases, particularly but not necessarily, chemical cases, where there is unpredictability in performance of certain species or subcombinations other than those specifically enumerated, one skilled in the art may be found not to have been placed in possession of a genus ...") *Regents of the University of California v. Eli Lilly & Co.*, 43 USPQ2d 1398.

MPEP § 2163 further states that if a biomolecule is described only by a functional characteristic, without any disclosed correlation between function and structure of the sequence, it is "not sufficient characteristic for written description purposes, even when accompanied by a method of obtaining the claimed sequence." MPEP § 2163 does state that for a generic claim the genus can be adequately described if the disclosure presents a sufficient number of representative species that encompass the genus. If the genus has a substantial variance, the disclosure must describe a sufficient variety of species to reflect the variation within that genus. See MPEP § 2163. Although the MPEP does not define what constitute a sufficient number of representative species, the courts have indicated what do not constitute a representative number of species to adequately describe a broad generic. In *Gostelli*, the courts determined that the disclosure of two chemical compounds within a subgenus did not describe that subgenus. *In re Gostelli*, 872, F.2d at 1012, 10 USPQ2d at 1618.

The factors considered in the Written Description requirement are (1) *level of skill and knowledge in the art*, (2) *partial structure*, (3) *physical and/or chemical properties*, (4) *functional characteristics alone or coupled with a known or disclosed correlation between structure and function*, and the (5) *method of making the claimed invention.* Disclosure of any combination of such identifying characteristics that distinguish the claimed invention from other

materials and would lead one of skill in the art to the conclusion that the applicant was in possession of the claimed species is sufficient." MPEP § 2163.

In the instant case, the claims are drawn to an isolated and purified polypeptide with a protein transduction domain which comprises SEQ ID NO: 1, and a complex comprising a polypeptide with a protein transduction domain linked to a cargo moiety, wherein the cargo moiety is selected from the group consisting of a small molecule, a nucleic acid, and a polypeptide.

(1) Level of skill and knowledge in the art:

The level of skill in this art is high, at least that of a doctoral scientist with several years of experience in the art.

(2) Partial structure: / (3) Physical and/or chemical properties:

The specification describes partial structure of the complex by disclosing the protein transduction domain as comprising SEQ ID NO: 1. The breadth of the complex is broad, because the cargo moiety can comprise any small molecule, nucleic acid, and any polypeptide, wherein the small molecules is selected from the group consisting of a radionuclide, a fluorescent marker, a dye, and a pharmaceutical agent.

(4) Functional characteristics:

The examples disclose the translocation of a complex comprising a polypeptide consisting of SEQ ID NO: 2 covalently linked with a biotin, and either an avidin conjugated β-galactosidase or avidin conjugated alkaline phosphatase that can transduce HEK 293 (human embryonic kidney), human umbilical vein endothelial, and NIH 3T3 fibroblast cells, but does not describe the functional characteristics of polypeptide comprising the protein transduction domain when other cargo moieties, as encompassed by the breadth of the currently claimed invention.

(5) Method of making the claimed invention:

The specification describes the synthesis of protein transduction domain with homo- and heterobifunctional cross-linkers to facilitate a complex formation with multiple reactive molecules, including biotin-avidin interaction.

As stated *supra*, the MPEP states that written description for a genus can be achieved by a representative number of species within a broad genus. Claims 1-3, 29, and 30 are broadly generic to all possible isolated and purified polypeptides located either on the amino- or carboxy-terminus of the protein transduction domain which comprises SEQ ID ON: 1. Claims 7-9, and 13 are broadly generic to all possible complexes, including fusion proteins encompassed by claim 13. The possible variations are enormous to any class of proteins. Since the MPEP states that if a biomolecule is described only by a functional characteristic, without any disclosed correlation between function and structure, it is "not sufficient characteristic for written description purposes, even when accompanied by a method of obtaining the claimed sequence." MPEP § 2163. Here, though the claims may recite some functional characteristics, the claims lack written description because there is no disclosure of a correlation between function and structure of fusion proteins linked to cargo moieties beyond those disclosed in the examples in the specification. Moreover, the specification lacks sufficient variety of species to reflect this variance in the genus since the specification does not provide any examples of fusion proteins besides fusions comprising a nuclear localization amino acid sequence.

While having written description of a complex comprising a polypeptide consisting of SEQ ID NO: 2 covalently linked with a biotin (SEQ ID NO: 1 with amino acid linker, including a lysine reactive side chain moiety), and either an avidin conjugated β-galactosidase or avidin conjugated alkaline phosphatase identified in the specification tables and/or examples, the

specification is devoid of any other proteins that are fused to the protein transduction domain that qualify for the functional characteristics claimed.

The description requirement of the patent statue requires a description of an invention, not an indication of a result that one might achieve if one made that invention. See *In re Wilder*, 736, F.2d 1516, 1521, 222 USPQ 369, 372-73 (Fed. Cir. 1984) (affirming rejection because the specification does "little more than outlin[e] goals appellants hope the claimed invention achieves and the problems the invention will hopefully ameliorate.") Accordingly, it is deemed that the specification fails to provide adequate written description for the genus of the claims and does not reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the entire scope of the claimed invention.

Conclusion

14. No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Anand U. Desai, Ph.D. whose telephone number is (571) 272-0947. The examiner can normally be reached on Monday - Friday 7:00 a.m. - 3:30 p.m..

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jon P. Weber can be reached on (517) 272-0925. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

February 15, 2006

JON WEBER
SUPERVISORY PATENT EXAMINER